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7) Polypeptide according to claim 5 corresponding to ORF8 represented in Figure 2 (having the sequence of SEQ ID No.5) and having a desosaminyltransferase activity, called EryCIII.

9) DNA sequence according to claim 8 comprising:

- 10 - the eryBIV sequence corresponding to ORF13 (sequence of SEQ
ID No.6 from nucleotide 242 to nucleotide 1207) and coding
for a dTDP-4-keto-L-6-desoxyhexose 4-reductase,
- the eryBV sequence corresponding to ORF14 (sequence of SEQ
ID No.6 from nucleotide 1210 to nucleotide 2454) and coding
15 for a mycarosyltransferase,
- the eryCVI sequence corresponding to ORF15 (sequence of SEQ
ID No.6 from nucleotide 2510 to nucleotide 3220) and coding
for a dTDP-D-6-desoxyhexose 3-N-methyltransferase,
- the eryBVI sequence corresponding to ORF16 (sequence of SEQ
20 ID No.6 from nucleotide 3308 to nucleotide 4837) and coding
for a dTDP-4-keto-L-6-desoxyhexose 2,3-deshydratase,
- the eryCIV sequence corresponding to ORF17 (sequence of SEQ
ID No.6 from nucleotide 4837 to nucleotide 6039) and coding
for a dTDP-D-6-desoxyhexose 3,4-deshydratase,
25 - the eryCV sequence corresponding to ORF18 (sequence of SEQ
ID No.6 from nucleotide 6080 to nucleotide 7546) and coding
for a dTDP-D-4,6-didesoxyhexose 3,4-reductase and
- the eryBVII sequence corresponding to ORF19 (sequence of
SEQ ID No.6 from nucleotide 7578 to nucleotide 8156) and
30 coding for a dTDP-4-keto-D-6-desoxyhexose 3,5 epimerase.
- 10) Isolated DNA sequence represented in Figure 3 chosen from
the eryBIV sequence corresponding to ORF13 (sequence of SEQ
ID No.6 from nucleotide 242 to nucleotide 1207), the eryBV
sequence corresponding to ORF14 (sequence of SEQ ID No.6 from
35 nucleotide 1210 to nucleotide 2454), the eryCVI sequence
corresponding to ORF15 (sequence of SEQ ID No.6 from
nucleotide 2510 to nucleotide 3220), the eryBVI sequence
corresponding to ORF16 (sequence of SEQ ID No.6 from

nucleotide 3308 to nucleotide 4837), the eryCIV sequence corresponding to ORF17 (sequence of SEQ ID No.6 from nucleotide 4837 to nucleotide 6039), the eryCV sequence corresponding to ORF18 (sequence of SEQ ID No.6 from nucleotide 6080 to nucleotide 7546) or the eryBVII sequence corresponding to ORF19 (sequence of SEQ ID No.6 from nucleotide 7578 to nucleotide 8156) and the sequences which hybridize and/or display significant homologies with this sequence or fragments of the latter and having the same function.

11) Isolated DNA sequence eryBV represented in Figure 3 corresponding to ORF14 (sequence of SEQ ID No.6 from nucleotide 1210 to nucleotide 2454) and coding for a mycarosyltransferase.

12) Polypeptide coded by one of the DNA sequences according to ~~one of claims 8 to 11.~~ ^{Claim 8}

13) Polypeptide according to claim 12 corresponding to an ORF represented in Figure 3, chosen from ORF13 (having the sequence of SEQ ID No.7), ORF14 (having the sequence of SEQ ID No.8), ORF15 (having the sequence of SEQ ID No.9), ORF16 (having the sequence of SEQ ID No.10), ORF17 (having the sequence of SEQ ID No.14), ORF18 (having the sequence of SEQ ID No.11) or ORF19 (having the sequence of SEQ ID No.12) and the analogues of this peptide.

14) Polypeptide according to claim 12 corresponding to ORF14 represented in Figure 3 (having the sequence of SEQ ID No.8) and having an mycarosyltransferase activity, called EryBV.

15) Use of at least one of the DNA sequences chosen from the sequences eryBII (complementary sequence of SEQ ID No.1 from nucleotide 48 to nucleotide 1046), eryCIII (complementary sequence of SEQ ID No.1 from nucleotide 1046 to nucleotide 2308) or eryCII (complementary sequence of SEQ ID No.1 from nucleotide 2322 to nucleotide 3404) represented in Figure 2, eryBIV (sequence of SEQ ID No.6 from nucleotide 242 to nucleotide 1207), eryBV (sequence of SEQ ID No.6 from nucleotide 1210 to nucleotide 2454), eryCVI (sequence of SEQ ID No.6 from nucleotide 2510 to nucleotide 3220), eryBVI (sequence of SEQ ID No.6 from nucleotide 3308 to nucleotide

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4837), *eryCIV* (sequence of SEQ ID No.6 from nucleotide 4837 to nucleotide 6039), *eryCV* (sequence of SEQ ID No.6 from nucleotide 6080 to nucleotide 7546) or *eryBVII* (sequence of SEQ ID No.6 from nucleotide 7578 to nucleotide 8156)

5 represented in Figure 3, to synthesize hybrid secondary metabolites in *Sac. erythraea*.

16) Use of at least one of the DNA sequences chosen from the sequences *eryBII* (complementary sequence of SEQ ID No.1 from nucleotide 48 to nucleotide 1046), *eryCIII* (complementary
10 sequence of SEQ ID No.1 from nucleotide 1046 to nucleotide 2308) or *eryCII* (complementary sequence of SEQ ID No.1 from nucleotide 2322 to nucleotide 3404) represented in Figure 2, *eryBIV* (sequence of SEQ ID No.6 from nucleotide 242 to nucleotide 1207), *eryBV* (sequence of SEQ ID No.6 from
15 nucleotide 1210 to nucleotide 2454), *eryCVI* (sequence of SEQ ID No.6 from nucleotide 2510 to nucleotide 3220), *ebryBVI* (sequence of SEQ ID No.6 from nucleotide 3308 to nucleotide 4837), *eryCIV* (sequence of SEQ ID No.6 from nucleotide 4837 to nucleotide 6039), *eryCV* (sequence of SEQ ID No.6 from
20 nucleotide 6080 to nucleotide 7546) or *eryBVII* (sequence of SEQ ID No.6 from nucleotide 7578 to nucleotide 8156) represented in Figure 3 or of a fragment of this sequence, as hybridization probes.

17) Use of the *eryCIII* DNA sequence represented in Figure 2
25 (complementary sequence of SEQ ID No.1 from nucleotide 1046 to nucleotide 2308 = complementary sequence of SEQ ID No.4) as a hybridization probe to isolate genes responsible for the glycosylation of the macrolactone in a macrolide-producing strain.

30 **18)** Use according to claim 17 in which the homologous genes are the oleandomycin biosynthesis genes in *S. antibioticus*.

19) Isolated DNA sequence represented in Figure 22 (sequence of SEQ ID No.15) corresponding to a region of the cluster of oleandomycin biosynthesis genes comprising:

- 35 - the sequence corresponding to ORF *oleP1* from nucleotide 184 to nucleotide 1386,
- the sequence corresponding to ORF *oleG1* from nucleotide 1437 to nucleotide 2714 coding for a glycosyltransferase

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activity,

- the sequence corresponding to ORF *oleG2* from nucleotide 2722 to nucleotide 3999 coding for a glycosyltransferase activity,

- 5 - the sequence corresponding to ORF *oleM* from nucleotide 3992 to nucleotide 4720 (= sequence of SEQ ID No.20) and
 - the sequence corresponding to ORF *oleY* from nucleotide 4810 to nucleotide 5967.

10 **20)** Isolated DNA sequence represented in Figure 22 chosen from the sequence corresponding to ORF *oleG1* (sequence of SEQ ID No.15 from nucleotide 1437 to nucleotide 2714 coding for a glycosyltransferase activity and the sequence corresponding to ORF *oleG2* (sequence of SEQ ID No.15 from nucleotide 2722 to nucleotide 3999) coding for a glycosyltransferase
 15 activity.

21) Isolated DNA sequence according to claim 20 corresponding to ORF *oleG1* (sequence of SEQ ID No.15 from nucleotide 1437 to nucleotide 2714) coding for a desosaminyltransferase activity.

20 **22)** Isolated DNA sequence according to claim 20 corresponding to ORF *oleG2* (sequence of SEQ ID No.15 from nucleotide 2722 to nucleotide 3999) coding for an oleandrosyltransferase activity.

25 **23)** Polypeptide coded by the DNA sequence corresponding to ORF *oleG1* and having a desosaminyltransferase activity (sequence of SEQ ID No.17).

24) Polypeptide coded by the DNA sequence corresponding to ORF *oleG2* and having an oleandrosyltransferase activity (sequence of SEQ ID No.18).

30 **25)** Process for the preparation of hybrid secondary metabolites in *Sac. erythraea* in which:

- a DNA sequence is isolated containing at least one *eryB* sequence or one *eryC* sequence of the cluster of erythromycin biosynthesis genes represented in Figure 2 (complementary
 35 sequence of SEQ ID No.1) or in Figure 3 (sequence of SEQ ID No.6),
 - a modification is created in said sequence and an altered sequence is obtained,

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- the altered sequence is integrated into the chromosome of the host strain and a modified strain is obtained,
- the modified strain is cultured under conditions which allow the formation of the hybrid secondary metabolite and
- 5 - the hybrid secondary metabolite is isolated.

26) Process according to claim 25 in which the DNA sequence codes for one of the enzymes chosen from a

- dTDP-4-keto-L-6-desoxyhexose 2,3-reductase,
- desosaminyltransferase,
- 10 - dTDP-4-keto-D-6-desoxyhexose 3,4-isomerase,
- dTDP-4-keto-L-6-desoxyhexose 4-reductase,
- mycarosyltransferase,
- dTDP-D-6-desoxyhexose 3-N-methyltransferase,
- dTDP-4-keto-L-6-desoxyhexose 2,3-deshydratase,
- 15 - dTDP-D-6-desoxyhexose 3,4-deshydratase,
- dTDP-D-4,6-didesoxyhexose 3,4-reductase or
- dTDP-4-keto-D-6-desoxyhexose 3,5 epimerase.

27) Process according to claim 25 in which the alteration of the sequence results in the inactivation of at least one of

- 20 the enzymes chosen from a
- dTDP-4-keto-L-6-desoxyhexose 2,3-reductase,
- desosaminyltransferase,
- dTDP-4-keto-D-6-desoxyhexose 3,4-isomerase,
- dTDP-4-keto-L-6-desoxyhexose 4-reductase,
- 25 - mycarosyltransferase,
- dTDP-D-6-desoxyhexose 3-N-methyltransferase,
- dTDP-4-keto-L-6-desoxyhexose 2,3-deshydratase,
- dTDP-D-6-desoxyhexose 3,4-deshydratase,
- dTDP-D-4,6-didesoxyhexose 3,4-reductase or
- 30 - dTDP-4-keto-D-6-desoxyhexose 3,5 epimerase.

28) Process according to claim 27 in which the inactivated enzyme is a dTDP-4-keto-L-6-desoxyhexose 4-reductase.

29) Process according to claim 27 in which the inactivated enzyme is a dTDP-D-6-desoxyhexose 3,4-deshydratase.

35 **30)** Process according to claim 27 in which the inactivated enzyme is a mycarosyltransferase.

31) Process according to claim 27 in which the inactivated enzyme is a dTDP-4-keto-L-6-desoxyhexose 2,3-reductase.

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32) Process according to claim 25 in which the isolated hybrid secondary metabolite is an analogue of erythromycin chosen from 4"-keto-erythromycin, 4'-hydroxy-erythromycin or 3"-C-desmethyl-2",3"-ene-erythromycin.

5 **33)** Process according to claim 25 in which the isolated hybrid secondary metabolite is desosaminyl erythronolide B.

34) Modified strain of *Sac. erythraea* in which at least one of the enzymes chosen from a

- dTDP-4-keto-L-6-desoxyhexose 2,3-reductase,

10 - desosaminyltransferase,

- dTDP-4-keto-D-6-desoxyhexose 3,4-isomerase,

- dTDP-4-keto-L-6-desoxyhexose 4-reductase,

- mycarosyltransferase,

- dTDP-D-6-desoxyhexose 3-N-methyltransferase,

15 - dTDP-4-keto-L-6-desoxyhexose 2,3-deshydratase,

- dTDP-D-6-desoxyhexose 3,4-deshydratase,

- dTDP-D-4,6-didesoxyhexose 3,4-reductase or

- dTDP-4-keto-D-6-desoxyhexose 3,5 epimerase

20 is inactivated and producing at least one hybrid secondary metabolite.

35) Modified strain of *Sac. erythraea* (BII92) in which a dTDP-4-keto-L-6-desoxyhexose 2,3-reductase is inactivated and producing 3"-C-desmethyl-2",3"-ene-erythromycin C.

25 **36)** Modified strain of *Sac. erythraea* (BIV87) in which a dTDP-4-keto-L-6-desoxyhexose 4-reductase is inactivated and producing 4"-keto-erythromycin.

37) Modified strain of *Sac. erythraea* (CIV89) in which a dTDP-D-6-desoxyhexose 3,4-deshydratase is inactivated and producing 4'-hydroxyerythromycin D.

30 **38)** Modified strain of *Sac. erythraea* (BV88) in which a mycarosyltransferase is inactivated and producing desoaminyl erythronolide B.

39) Preparation process for precursors of oleandomycin in *S. antibioticus* in which

35 - an alteration is created in the sequence of the gene chosen from the DNA sequence corresponding to ORF *oleG1* (sequence of SEQ ID No.15 from nucleotide 1437 to nucleotide 2714) and the DNA sequence corresponding to ORF *oleG2* (sequence of

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5 - the modified strain is cultured under conditions allowing
the accumulation of the precursors of oleandomycin and
- these precursors are isolated.

41) Thymidine 5'-(trihydrogen diphosphate), P'-[3,4,6-trideoxy-3-(dimethylamino)-D-.xylo.-hexopyranosyl] ester (dTDP-D-desosamine) and the addition salts with bases.

add c'

add c^4